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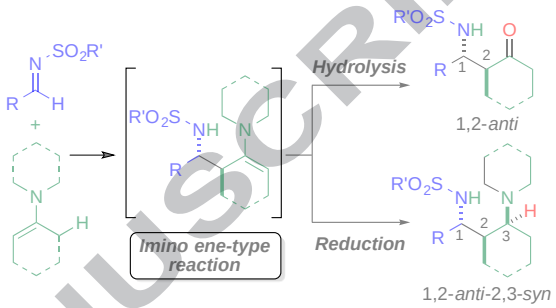

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Imino ene-type reaction of enamines with *N*-sulfonylimines and application to diastereoselective synthesis of *N*-sulfonyl-1,3-diamines

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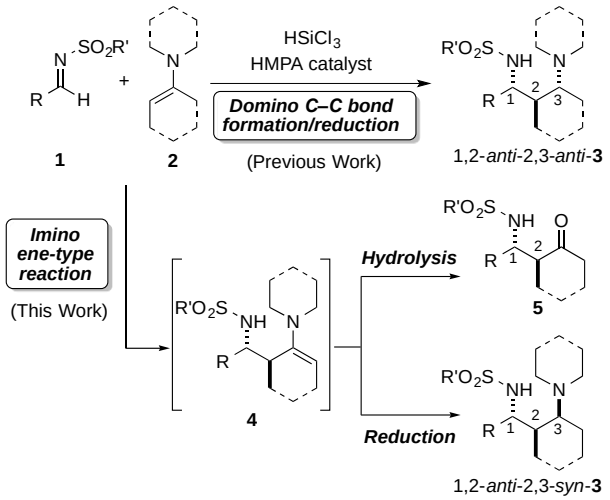
ABSTRACT

Enamines react rapidly with *N*-sulfonylimines to afford imino ene-type adducts. The reaction proceeds even at –78 °C in the presence of acetic acid and shows high diastereoselectivity. Acid hydrolysis of imino ene-type products affords β-amino ketones, and reduction with $NaBH_3CN$ furnishes *N*-sulfonyl-1,3-diamines with high diastereoselectivities. The stereochemistry of these transformations is considered based on transition state models.

Enamines are powerful enolate equivalents in organic synthesis and are widely utilized in alkylations, acylations, and Michael additions.[1] However, reactions of enamines with *imines* are limited. In 1969, Nomura *et al.* reported that cyclohexanones/morpholine-derived enamines slowly reacted with benzaldehyde/aniline-derived imines in methanol to afford imino ene-type adducts in low yields.[2,3] Later, they also found other transformations via [2+2] cycloaddition between enamines and *N*-arylimines in acetic acid.[4] In 1975, Marchetti *et al.* revealed that 2-phenyl-3*H*-indol-3-one reacted reversibly with cyclohexanone-derived enamines to afford imino ene-type products.[5] They proposed a synchronous mechanism to explain the position of the double bond of the enamine products. Recently, Dixon *et al.* reported chiral biphenol-catalyzed enantioselective Mannich-type reaction of *N*-Boc-imines with aryl methyl ketones-derived enamines.[6]

We have more recently found that a domino reaction of *N*-sulfonylimines **1**, enamines **2**, and trichlorosilane in the presence of HMPA as a Lewis base catalyst provides *N*-sulfonyl-1,3-diamines **3** with high 1,2-*anti*-2,3-*anti* diastereoselectivity (Scheme 1, the first equation).[7] In the course of this study, we unexpectedly found that imines **1** and enamines **2**, in the absence of trichlorosilane and the catalyst, underwent a rapid imino ene-type reaction to afford enamines **4**. Acid hydrolysis of **4** afforded 1,2-*anti*-β-amino ketones **5** (Scheme 1, the second equation). Meanwhile, reduction of **4** with $NaBH_3CN$ afforded 1,2-*anti*-2,3-*syn*-*N*-sulfonyldiamines **3** with a stereochemistry that differed from that observed in the domino reaction with trichlorosilane[7] (Scheme 1, the third equation). This communication reports these findings.



Scheme 1. Imino ene-type reaction of *N*-sulfonylimines **1** and enamines **2** and transformations of imino ene-type products **4**.

Initially, we monitored the reaction of benzaldehyde-derived *N*-tosylimine **1a** and cyclohexanone/piperidine-derived enamine **2a** by ^{1}H-NMR spectroscopy (Eq 1). After the addition of enamine **2a** to a solution of imine **1a** in CD_2Cl_2 at 0 °C, the instant generation of imino ene-type adduct **4aa** was observed with good diastereoselectivity (*anti*/*syn* = 88/12).[8] According to Mayr's reactivity scale, the second order kinetic constant ($k_{20\,°C}$)

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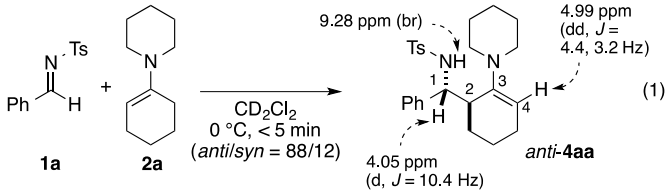
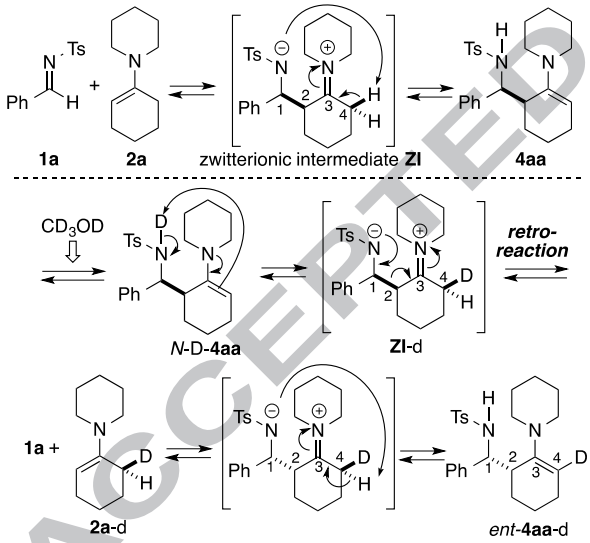
for C–C bond formation between imine **1a** and enamine **2a** can be estimated to be 32.1 $Lmol^{-1}s^{-1}$ (>99% conversion within 10 s at 20 °C).[9] Representative ^{1}H-NMR data of *anti*-**4aa** are shown in Eq 1. The broad peak at 9.28 ppm was assigned to the amide proton bound intramolecularly to the piperidino nitrogen, as it disappeared quickly upon addition of CD_3OD. Interestingly, this deuteration experiment revealed that the H4 olefin proton was also gradually substituted by deuterium.[8,10]

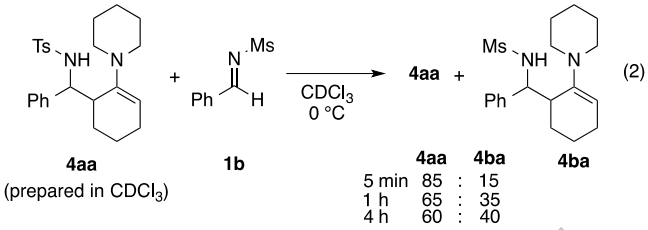


Because enamine **2a** alone was not deuterated by CD_3OD, we speculated that the tosylamide group intramolecularly delivered the deuterium atom to the 4-position. Scheme 2 illustrates the proposed reaction mechanism. Nucleophilic addition of **2a** to **1a** affords a zwitterionic intermediate **ZI**, and the amide anion abstracts the hydrogen at the 4-position intramolecularly to afford imino ene-type product **4aa**. Upon addition of CD_3OD, the amide hydrogen of **4aa** is quickly exchanged with a deuterium to afford *N*-D-**4aa**, which then delivers the deuterium atom to the 4-position, forming deuterated zwitterionic intermediate **ZI**-d. Because the amide anion of **ZI**-d cannot abstract the *trans* proton at the 4-position, the *retro*-imino ene-type reaction of **ZI**-d may proceed to generate deuterated enamine **2a**-d, which then reacts again with imine **1a** from the side *anti* to the deuterium atom to afford the deuterated product *ent*-**4aa**-d.

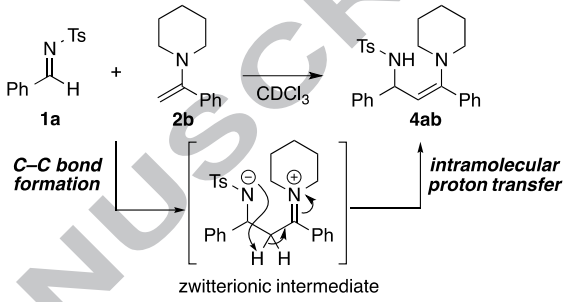


Scheme 2. Assumed mechanism for imino ene-type reaction and deuterium incorporation.

To prove the reversibility assumed above, *N*-mesylimine **1b** was added to the product **4aa** prepared in $CDCl_3$, and the reaction was monitored by ^{1}H-NMR analysis (Eq 2).[8] Rapid generation of the corresponding *N*-mesylimine adduct **4ba** was observed, and the **4aa** to **4ba** ratio was almost constant after 4 h.[11] These observations clearly support the reversibility of the process.



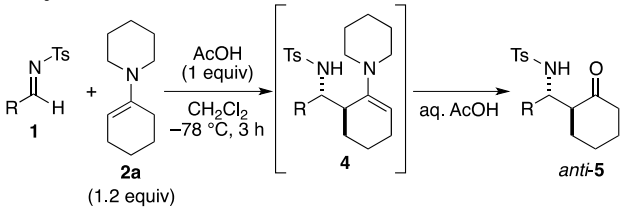
Meanwhile, the reaction of imine **1a** with acetophenone-derived enamine **2b**, bearing no allylic proton, proceeded rapidly to afford enamine **4ab** (Scheme 3).[8] This result supports the stepwise mechanism *via* a zwitterionic intermediate (Scheme 2) rather than a concerted mechanism.



Scheme 3. The reaction of imine **1a** and enamine **2b**.

Having these mechanistic insights in mind, imino ene-type reactions between various *N*-sulfonylimines **1** with enamine **2a** were investigated (Table 1). To evaluate the reaction efficiency, imino ene-type products **4** were converted to β-amino ketones **5** by hydrolysis using aqueous acetic acid. The reaction of imine **1a** with enamine **2a** proceeded even at −78 °C and showed an improved *anti* selectivity (*anti*/*syn* = 94/6), although the reaction time was extended to 21 h (entry 1). Addition of acetic acid (1 equiv) effectively shortened the reaction time (3 h) without decreasing the diastereoselectivity (entry 2). This additive was also effective for the reaction of other imines with enamine **2a** (entries 3–9). *N*-Mesylimine **1b** required a longer reaction time (6 h), but provided somewhat higher selectivity than **1a** (entry 3). With slight modifications of the reaction temperature and/or time according to their electronic and steric nature, aromatic *N*-tosylimines **1c**–**g** afforded the corresponding β-amino ketones in high yields and diastereoselectivities (entries 4–8). Whereas cinnamaldehyde-derived *N*-tosylimine **1h** exhibited a low diastereoselectivity (entry 9), cyclohexanecarboxaldehyde- and 3-phenylpropanal-derived imines **1i** and **1j** provided high *anti* selectivities (entries 10 and 11). Acetic acid was not added in the latter cases to suppress the decomposition of imines **1i** and **1j** with the acid. These results indicate that the bulkier the R group of imine **1** is, the higher the diastereoselectivity is.

Table 1. Imino ene-type reactions between various *N*-sulfonylimines **1** and enamines **2**[a]

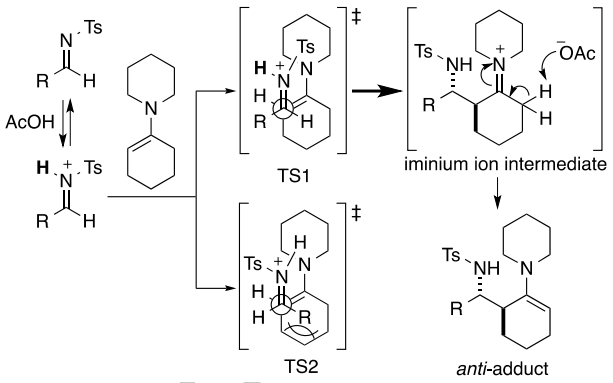


Entry	R (**1**)	**5**	Yield (%)	*anti*/*syn*
1[b,c]	Ph (**1a**)	**5aa**	82	94/6
2	Ph (**1a**)	**5aa**	89	95/5
3[d]	Ph (**1b**)[e]	**5ba**	96	96/4
4[f]	*p*-$O_2NC_6H_4$ (**1c**)	**5ca**	90	97/3

5[g]	*p*-MeOC$_6$H$_4$ (**1d**)	**5da**	97	93/7
6	2-naphthyl (**1e**)	**5ea**	95	97/3
7[f,g]	1-naphthyl (**1f**)	**5fa**	82	>99/1
8	2-furyl (**1g**)	**5ga**	91	93/7
9	(*E*)-PhCH=CH (**1h**)	**5ha**	67	66/34
10[b,g]	cyclohexyl (**1i**)	**5ia**	50	99/1
11[b,g]	Ph(CH$_2$)$_2$ (**1j**)	**5ja**	76	99/1

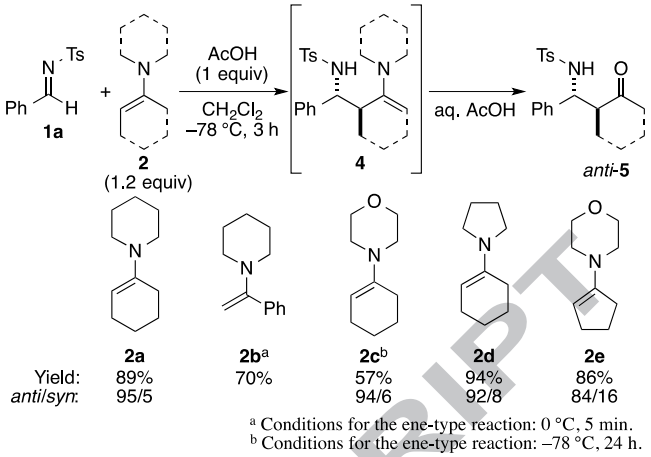
[a] Unless otherwise noted, the reaction of an imine **1** (0.5 mmol) and enamine **2a** (1.2 equiv) was conducted in the presence of AcOH (1 equiv) at –78 °C for 3 h. The reaction mixture was then quenched by treatment with aqueous acetic acid at rt.
[b] Without acetic acid.
[c] For 21 h.
[d] For 6 h.
[e] *N*-Mesylimine (**1b**) was used instead of **1a**.
[f] For 24 h.
[g] At –45 °C.

At low temperature, the imino ene-type reaction would not be under equilibrium but kinetically controlled, because the diastereomeric ratio of **4aa**, generated from **1a** and **2a** at 0 °C (*anti*/*syn* = 88/12), was not changed after standing at –78 °C for 3 h with acetic acid (1.0 equiv). Thus, the stereochemistry can be rationalized as shown in Scheme 4. The acetic acid protonates and activates the imine. The enamine adds to the resulting iminium ion *via* transition states TS1 or TS2. TS1 would presumably be more stable than TS2 because of the lower steric repulsion of the R group, resulting in the *anti* iminium ion intermediate. Then deprotonation by the acetate anion would furnish the *anti* imino ene-type product. When the R group is as bulky as 1-naphthyl, TS1 becomes exclusive (Table 1, entry 7). On the other hand, TS2, leading to the *syn* product, becomes competitive when the R group is as small as PhCH=CH, thus lowering the selectivity (Table 1, entry 9).



Scheme 4. Transition state models for the imino ene-type reaction in the presence of acetic acid.

The scope and limitation of enamines were next examined for the reaction with imine **1a** (Scheme 5). Cyclohexenylamines **2a**, **2c**, and **2d** provided high diastereoselectivities, whereas cyclopentenylamine **2e** showed a lower selectivity. TS2 in Scheme 4 would become more competitive in the case of **2e**, because the cyclopentenyl group interferes less with the R group than the cyclohexenyl group.

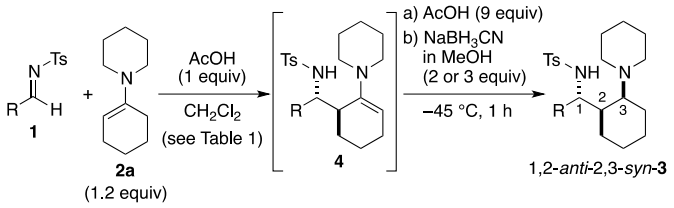


[a] Conditions for the ene-type reaction: 0 °C, 5 min.
[b] Conditions for the ene-type reaction: –78 °C, 24 h.

Scheme 5. The reaction of imine **1a** and various enamines **2**.

To utilize the enamine moiety of the imino ene products **4**, reduction to the *N*-sulfonyl-1,3-diamines **3** was next investigated.[12,13] It turned out that **4aa** prepared *in situ* from **1a** and **2a** could be reduced by treatment with acetic acid (9 equiv) and $NaBH_3CN$[14] (2 equiv) at –45 °C to afford 1,2-*anti*-2,3-*syn*-*N*-sulfonyl-1,3-diamine **3aa** with high diastereoselectivity (Table 2, entry 1).[15] Notably, the stereochemical outcome differs from that of the domino reaction using trichlorosilane reported previously.[7,16] With a slight modification of the amount of reductant and/or the reaction temperature, the reaction of other aromatic imines **1b**–**e**, **1g**, **1i**, and **1j** also furnished the corresponding 1,2-*anti*-2,3-*syn*-*N*-sulfonyldiamines **3** with high yields and diastereoselectivities (entries 2–8). It should be noted that the observed diastereoselectivity in the C–C bond formation was retained under the reduction conditions (Tables 1 and 2).

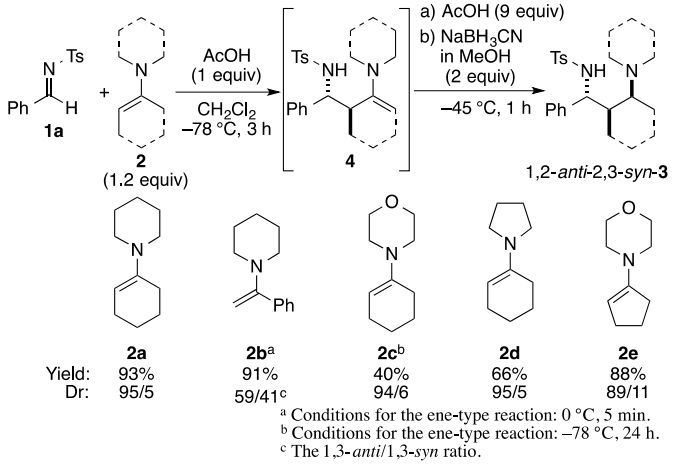
Table 2. Synthesis of *N*-sulfonyl-1,3-diamines **3** from various *N*-tosylimines **1** and enamine **2a**[a]



Entry	R (**1**)	**3**	Yield (%)	Dr[b]
1[c]	Ph (**1a**)	**3aa**	93	95/5
2[c]	Ph (**1b**)[d]	**3ba**	92	96/4
3[e]	*p*-$O_2NC_6H_4$ (**1c**)	**3ca**	90	96/4
4[c]	*p*-MeOC$_6$H$_4$ (**1d**)	**3da**	87	96/4
5[c,f]	2-naphthyl (**1e**)	**3ea**	97	97/3
6[e,f]	2-furyl (**1g**)	**3ga**	84	94/6
7	cyclohexyl (**1i**)	**3ia**	80	93/7
8[c]	Ph(CH$_2$)$_2$ (**1j**)	**3ja**	75	99/1

[a] Unless otherwise noted, the reaction of an imine **1** (0.5 mmol) and enamine **2a** (1.2 equiv) was conducted under the conditions shown in Table 1. Acetic acid (9 equiv) and sodium cyanoborohydride (2 or 3 equiv) in methanol were successively added, and the reaction mixture was stirred at –45 °C for 1 h before workup.
[b] Dr = 1,2-*anti*-2,3-*syn*-isomer/1,2-*syn*-2,3-*syn*-isomer. The other isomers were not observed. See ref 15.
[c] With $NaBH_3CN$ (2 equiv).
[d] *N*-Mesylimine (**1b**) was used instead of **1a**.
[e] With $NaBH_3CN$ (3 equiv).
[f] At 0 °C for the reduction step.

The scope and limitation of enamines in the *N*-sulfonyl-1,3-diamine synthesis using imine **1a** were also examined (Scheme 6). Although enamine **2b** provided a low diastereoselectivity, enamines **2a**, **2c**, **2d**, and **2e** exhibited high diastereoselectivities, as observed in the C–C bond formation/hydrolysis (Schemes 5 and 6)



Scheme 6. *N*-Sulfonyl-1,3-diamine synthesis from imine **1a** and various enamines **2**.

The stereochemistry of the reduction can be rationalized by assuming an axial attack of $NaBH_3CN$ on the iminium ion intermediate (Figure 1).[16] Because of the allylic strain between the piperidine ring, the tosylamide side chain locates in the axial position and hinders the equatorial attack of the reductant. The cycloalkane moiety should be important to fix the conformation of the iminium ion intermediate, because the reaction of enamine **2b** resulted in a low selectivity (Scheme 6).

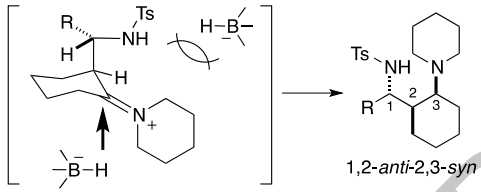


Fig 1. Assumed transition state.

In summary, we have demonstrated that *N*-sulfonylimines and enamines undergo an imino ene-type reaction smoothly with a high diastereoselectivity. Hydrolysis and reduction of the imino ene products afforded 1,2-*anti*-β-amino ketones and 1,2-*anti*-2,3-*syn*-*N*-sulfonyldiamines, respectively, without decreasing the high diastereoselectivities. Asymmetric catalysis and the extension of this method to reactions with various electrophiles other than imines are currently under investigation.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version at...

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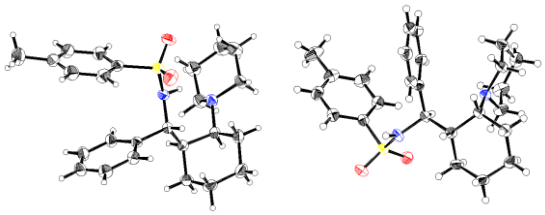
15. The relative configurations of both the major and second major diastereomers of **3aa** were unambiguously determined by X-ray crystallography to be 1,2-*anti*-2,3-*syn* (Figure, left) and 1,2-*syn*-2,3-*syn* (Figure, right), respectively. CCDC 991772 (1,2-*anti*-2,3-*syn*-**3aa**) and CCDC 991773 (1,2-*syn*-2,3-*syn*-**3aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



16. The addition of trichlorosilane to imino ene-type product **4aa** (in CH_2Cl_2 at 0 °C for 1 h) afforded 1,2-*anti*-2,3-*anti*-*N*-sulfonyldiamine **3aa** in low yield (26%). Higher yield (68%) was obtained when enamine **2a** was added to a solution of imine **1a** and trichlorosilane under the same conditions. Therefore, we believe that imino ene-type product **4aa** is not the predominant intermediate for the domino reaction using trichlorosilane (ref. 7). In this domino reaction, the silane tethering to the tosylamide side chain would reduce the iminium ion intermediate to afford the 1,2-*anti*-2,3-*anti*-*N*-sulfonyl-diamine as shown below.